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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/518,771	10/27/2005	Paul Stroobant	50189/003002	4907

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EXAMINER	
LUNDGREN, JEFFREY S	
ART UNIT	PAPER NUMBER
1639	

NOTIFICATION DATE	DELIVERY MODE
08/29/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/518,771	STROOBANT ET AL.	
	Examiner	Art Unit	
	JEFFREY S. LUNDGREN	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-52* is/are pending in the application.

4a) Of the above claim(s) *32, 34, 36, 49 and 51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-31,33,35,37-48,50 and 52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/9/06; 9/14/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' Election

Applicant's election without traverse of the elected species in the reply filed on May 14, 2008, is acknowledged.

Claims 1-52 are pending in the instant Application; claims 32, 34, 36, 49 and 51 are withdrawn as being directed to non-elected species; claims 1-31, 33, 35, 37-48, 50 and 52 are the subject of the Office Action below.

Oath/Declaration

The Declaration filed on October 27, 2005, is objected because it does not identify the mailing address of each inventor. A mailing address is an address at which an inventor customarily receives his or her mail and may be either a home or business address. The mailing address should include the ZIP Code designation. The mailing address may be provided in an application data sheet or a supplemental oath or declaration. See 37 CFR 1.63(c) and 37 CFR 1.76.

Information Disclosure Statement

The information disclosure statements (IDSs) submitted on August 9, 2006, and September 14, 2007, have been considered by the Examiner. The submission submitted on August 9, 2006, is in compliance with the provisions of 37 CFR § 1.97. Enclosed with this Office Action is a return-copy of this Form PTO-1449 with the Examiner's initials and signature indicating those references that have been considered.

The submission submitted on September 14, 2007, does not comply with 37 C.F.R. § 1.98(b)(5), because the date of publication (or public availability) is not listed on Form-1449. Accordingly, this reference has been lined through.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7-10, 12-16, 21, 27, 28, 30, 31, 35, 38, 39, 41, 42, 46, 47 and 52, are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 7, 9, 13 and 15 are indefinite for lack of proper antecedent basis because the phrase "said controlling" does not appear to be the same "controlling" of claim 6. For example, in claim 6, the "controlling" refers to the binding species, whereas the "controlling" in claims 7 and 9 refers to the first biological sample on the matrix.

Claims 8, 10, 14 and 16, are indefinite for lack of proper antecedent basis because the claims recite repeating steps (a) - (k) or steps (c) – (k), however, claim 1 only has steps (a) - (d). Applicants may overcome this rejection, for example, by amending the claims to depend from or claim 4, either directly or indirectly.

Claim 12 is indefinite for lack of proper antecedent basis because the claim refers to step (e), yet does not depend from a claim that establishes step (e), such as claim 2. Instead, claim 12 depends from claim 11, which in turn depends from claim 1.

Claims 21, 41, 42, 47 and 52, are indefinite for reciting the phrase "said biomolecule" because it is not clear if Applicants are referring to the "first biomolecule" or the "second biomolecule."

Claim 27 is indefinite for reciting the phrase "said peptide-nucleic acid library" because there is no antecedent basis in claim 1.

Claim 28 is indefinite for reciting the phrase "said phage display library" because there is no antecedent basis in claim 1.

Claim 30 is indefinite for reciting the phrase "said first and second organisms are human" because there is no antecedent basis in claim 1.

Claim 31 is indefinite for reciting the phrase "said first organism" and "said second organism" because there is no antecedent basis in claim 1.

Claim 35 is indefinite for reciting the phrase "said body fluid" because there is no antecedent basis.

Claim 37 is indefinite for reciting the phrase "said organ" because there is no antecedent basis.

Claims 38, 39 and 46, are indefinite for reciting "said third support" because there is no antecedent basis in claim 1.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 5-7, 11-13, 17, 18, 21-31, 33, 35, 37-39, 43, 44, 47, 48 and 52, are obvious over Cai in view of Lueking:

Claims 1-3, 5-7, 11-13, 17, 18, 21-31, 33, 35, 37-39, 43, 44, 47, 48 and 52, are rejected under 35 U.S.C. 103(a) as being obvious over Cai *et al.*, *Proc. Natl. Acad. Sci.*, *92*:6537-6541 (**1995**), in view of Lueking *et al.*, *Current Genomics*, *2*:151-159 (**2001**).

Claim 1 is directed towards a method for determining an abundance of a biomolecule in a biological sample, said method comprising the steps of:

(a) adhering a first biological sample to a first support to create a first matrix comprising one or more biomolecules from said first sample;

(b) adhering a second biological sample to a second support to create a second matrix comprising one or more biomolecules from said second sample;

(c) exposing a library of binding species at least one time to said first matrix to create a first product comprising one or more binding species of said library; and

(d) exposing the first product at least one time to said second matrix to create a second product, wherein a binding species present or absent in said second product is indicative of the abundance of said biomolecule in said first biological sample relative to said second biological sample.

Cai teaches the construction of fusion libraries that produce single-chain Fv antibodies from peripheral blood lymphocytes of two melanoma patients who had been immunized with

autologous melanoma cells transduced with the γ-interferon gene to enhance immunogenicity. Anti-melanoma antibodies were selected from each library by panning the phage against live cultures of the autologous tumor. After two or three rounds of panning, clones of the phage were tested by ELISA for binding to the autologous tumor cells; >90% of the clones tested showed a strong ELISA reaction, demonstrating the effectiveness of the panning procedure for selecting antimelanoma antibodies. As in step (a) of claim 1, a first biological sample of is adhered to a solid support to create a first matrix comprising one or more biomolecules, namely, the immobilization of the melanoma cells attaches as a monolayer in the flask wherein the melanoma cells display their surface bound proteins; and as in step (c), a library of binding species is exposed to the to the first matrix to create a first product, namely, the phage library is reacted with the melanoma cells that are adhered on the support:

> "The autologous melanoma lines were grown as an attached monolayer in 24-cm^2 flasks until almost confluent, and after changing the culture medium three times, the cells were incubated for 1 hr at 37°C. For the first panning step, the phage from a scFv library were precipitated in 4% (wt/vol) PEG/0.5 M NaCl and resuspended in water, and $\approx 10^{11}$ transforming units were added to the autologous melanoma cells in 2 ml of DMEM/10% fetal calf serum. The culture flask was shaken gently for 2 hr at room temperature, and then the medium was removed and the cells were washed rapidly 10 times with phosphate-buffered saline (PBS) at room temperature. The phage that remained attached were eluted from the cells in 2.0 ml of E-buffer (0.1 M glycine, pH 2.2/0.1% bovine serum albumin) for 10 min at room temperature and neutralized with 0.375 ml of N-buffer (1 M Tris HCl, pH 9.1). The eluted phage were mixed with 15 ml of logarithmic-phase Escherichia coli K91 Kan cells, and after 30 min at room temperature the cells were plated on 2x TY agar/tetracycline at 12.5 μg/ml to amplify the phage. For each subsequent panning step the amplified phage from the previous panning step were precipitated in 4% PEG/0.5 M NaCl and resuspended in water, and 101 phage were used to pan against autologous melanoma cells as described for the first panning step."

Cai, page 6539, col. 1, section titled, *Panning a scFv Library*.

As in step (b) of claim 1, a second biological sample is adhered and forms a second matrix, of one or more biomolecules from the second sample, namely, melanocytes were grown and fixed to a support and display their surface bound proteins:

> "Melanocytes were grown in 35-mm culture dishes until a confluent layer had formed, and the cells were then fixed with gluteraldehyde [*sic*] as described for the ELISA reaction and blocked with DMEM/10% fetal calf serum. After panning, ≈ 10% of the unamplified phage was added to the melanocytes in DMEM/10% fetal calf serum and kept at room temperature for 1 hr with gentle shaking. The unabsorbed phage were then transferred to a fresh culture dish containing fixed melanocytes, and the procedure was repeated. After 10 such absorption steps the unabsorbed were cloned."

Cai, page 6539, col. 2, section titled, *Absorption Against Melanocytes*.

As in claim 5, the bound phage to the cells disclosed in Cai, consist essentially of one or more binding species that bind to the first matrix (see description of Cai above); as in claims 43 and 44, the panning steps of Cai include multiple exposures of the phage (see captioned text of Cai above). As in claim 11, the phage eluted phage from the melanoma that bind to the melanocyte consist essentially of one or more binding species that bind to the second matrix.

As in claim 6, Cai controls the relative amount of the scFv library members introduced to the cells in the first panning step, namely, introduces the amount of about 10^{11} transforming units (page 6539, col. 1, section titled, *Panning a scFv Library*).

As in claim 21, Cai teaches that the biomolecules are proteins, such as the surface proteins/antigens from melanocytes and melanoma that the library of antibodies bind (page 6539, col. 1; also page 6540, col. 2, section titled, *Discussion*).

As in claims 26-28, Cai teaches the use of a phage library that display peptides (*i.e.*, antibodies – page 6539, col. 1, section titled, *Panning a scFv Library*).

As in claim 29-31, 33 and 37, Cai teaches that the first biological sample and the second biological samples are the various cells, specifically, the cultured melanocyte cells and melanoma cells, which are isolated from different organisms, both organisms are human, and one is healthy while the other is diseased; Cai also teaches pancreatic cells and ovary cells (page 6539, col. 1, section titled, *Human Cells*).

Although Cai teaches his method can be used for qualitative determination of library members that are selective for melanoma compared to melanocytes, Cai does not explicitly state that the binding species present in the second product is indicative of the abundance of the biomolecule in the first biomolecule sample relative to the second sample, as in claim 1. Neither

does Cai explicitly suggest providing a complementary step of exposing the library to the second matrix and then the first matrix (*i.e.*, repeating steps (c) and (d), but reversing the first and second matrix for complete differential expression), as in claims 2 and 3, and the dependent limitations as set forth in dependent claims 12-18, 39 and 44. Nor does Cai teach arrays, as in claim 21, or the other limitations in the claims as detailed below.

Lueking provides a review of proteomics research, including a discussion of the methods used in the art to characterize the differential expression of proteins between two different tissues, such as healthy and diseased tissues (page 152, paragraph bridging columns 1 and 2), including subtracted library generation. Lueking also discusses how immunoassays are used to quantify the corresponding target/antigen using libraries of antibodies or phage (page 156, column 1, first full paragraph), and the application with protein arrays (page 157, column 2, final paragraph). As in claim 7, Lueking teaches the use of a protein array with dilutions of the biological matrix (page 155, col. 2, near the bottom of the column).

As in claim 21, Lueking teaches that the biomolecules are proteins, such as the proteins in a protein array (page 152, col. 2). As in claims 22 and 24, Lueking teaches that the biomolecules of the profile being studied are attached to the surface of the bioassay device (Lueking, page 154, col. 1, second full paragraph – wherein Yang is cited for attachment;[1] Yang teaches that biomolecules are first derivatized with streptavidin for binding to biotinylated surfaces, or biotin-streptavidin-biotin attachment). As in claims 23 and 25, the extent of the derivatization (*i.e.*, density) is controlled by the type of derivatizing agent (Lueking's reference to Yang, Yang at page 1754, paragraph bridging cols. 1 and 2). In this same section Lueking, Lueking also teaches covalent attachment of the biomolecules to the support matrix, as in claims 38 and 39.

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[1] Since Yang (Yang *et al.*, *Langmuir*, *16*:1751-1758 (**2000**)) is effectively incorporated by reference into the teaching of Lueking, in particular the teachings as it pertains to derivatizing biomolecules for immobilization, Lueking is treated as teaching these limitations. *See*, *Advanced Display Systems Inc. v. Kent State University*, 54 USPQ2d 1673 at 1679 (Fed. Cir. 2000) – "Incorporation by reference provides a method for integrating material from various documents into a host document --a patent or printed publication in an anticipation determination-- by citing such material in a manner that makes clear that the material is effectively part of the host document as if it were explicitly contained therein. *In re Saunders*, 444 F.2d 599, 602-03, 170 USPQ 213, 216-17 (CCPA 1971) (reasoning that a rejection for anticipation is appropriate only if one reference "expressly incorporates a particular part" of another reference.

As in claims 26-28, Lueking teaches the use of a phage library that display peptides (i.e., antibodies; see Lueking at page 156, first full paragraph.

As in claim 35, Lueking teaches that the biomolecules may be obtained from samples of blood or urine (Lueking at page 156, first full paragraph) – this section of Lueking also teaches the use of mass spectrometry, as in claim 48. Lueking further teaches that the differential analysis is useful for determining the presence of a disease state (page 155, col. 1, second paragraph), as in claim 52. This section of Lueking also teaches a chip (see also, page 155, Figure 1), as in claim 47.

One of ordinary skill in the art would have had a reasonable expectation of success in arriving at the invention as claimed because each of Cai and Lueking are directed towards the use of phage libraries for determining the differential expression pattern between healthy and disease samples. One of ordinary skill in the art would have recognized the advantages of using a quantitative approach of Lueking in addition to the qualitative identification of Cai because of the adding understanding that expression levels provide in understanding the disease pathologies. Additionally, Lueking further elaborates on how differential expression approaches are suited to either whole cells or tissue extracts (page 156, col. 1, first full paragraph).

Furthermore, in reference to claims 2 and 3, based on the teaching of Cai where the library of phage is first bound to the melanoma and then eluted and bound to the melanocytes for identifying phage that identify for melanoma-specific surface proteins, one of ordinary skill in the art would have also recognized the advantages of the reverse screening process. Namely, binding a library of phage to the melanocytes followed by treating the eluted phage to the melanoma sample to identify and quantify melanocyte-specific proteins. Not only would doing so provide a comprehensive understanding of both tissues' proteins and yield a full profile of the differentially-expressed proteins between the melanoma and melanocytes, but further amounts to a reversal of parts based on Cai's teachings; see *In re Gazda*, 219 F.2d 449, 104 USPQ 400 (CCPA 1955), where the prior art disclosed a clock fixed to the stationary steering wheel column of an automobile while the gear for winding the clock moves with steering wheel; mere reversal of such movement, so the clock moves with wheel, was held to be an obvious expedient. In reference to claim 12 and 13, one of ordinary skill in the art would have found the controlling the relative amount of binding species to the second matrix in the analysis of the melanocyte-specific

proteins, as well as the use of dilutions for optimized quantitative analysis to be obvious for the same reasons as in claims 6 and 7 detailed above. In reference to claims 17 and 18, by also reacting the library with the melanocytes for comparing the second half of the differential binding profile, the limitations of claim 17 are met (*i.e.*, third product consists essentially of one or more binding species that bind to said second matrix), and the eluted library members from the melanocytes members that bind the melanoma meet the limitations of claim 18 (*i.e.*, the fourth product consists essentially of the one or more binding species that bind to said first matrix). In reference to claim 44, Cai teaches a panning process which includes repeat exposure of the biomolecules to the phage, and therefore the full differential assay where the melanocytes are first screened with the phage library followed by binding to the melanocytes meets the required limitations.

Claims 1-3, 5-18, 21-31, 33, 35, 37-39, 43, 44, 47, 48 and 52, are obvious over Cai, Lueking and Fowlkes:

Claims 1-3, 5-18, 21-31, 33, 35, 37-39, 43, 44, 47, 48 and 52, rejected under 35 U.S.C. 103(a) as being unpatentable over Cai *et al.*, *Proc. Natl. Acad. Sci.*, *92*:6537-6541 (**1995**), in view of Lueking *et al.*, *Current Genomics*, *2*:151-159 (**2001**), as applied to claims 1-3, 5-7, 11-13, 17, 18, 21-31, 33, 35, 37-39, 43, 44, 47, 48 and 52, above, and further in view of Fowlkes *et al.*, U.S. Patent No. 6,617,114, issued on September 9, 2003.

The limitations of claims 1-3, 5-7, 11-13, 17, 18, 21-31, 33, 35, 37-39, 43, 44, 47, 48 and 52, and the corresponding teachings of Cai and Lueking are set forth above, and are hereby incorporated into the instant rejection.

Although Cai and Lueking teach differential expression techniques using protein capture assays with phage, neither Cai nor Lueking expressly suggests using the particular dilution in the determination steps as in claims 8-10 and 14-16.

Fowlkes is directed to the identification of compounds in a compound library which can mediate the biological activity of a target receptor protein, wherein the library members include phage. Fowlkes teaches the use of phage in a panning experiment for identifying members that bind to a given series of targets, wherein the phage are then bound to the immobilized DH5αF'

through a series of dilutions (col. 34, lines 42-57). In doing so, Fowlkes is able to find the appropriate analytical ranges for titer approximation.

One of ordinary skill in the art would have had a reasonable expectation of success in arriving at the invention as claimed because each of Cai, Lueking and Fowlkes are directed to the use of a library of phage for identifying target binding members. One of ordinary skill in the art would have been motivated to utilize a serial dilution approach (*e.g.*, reiterating dilutions as in claims 8-10, and applied to claims 14-16 for the second matrix) as taught in Fowlkes with the approach of Cai and Lueking for analyzing the target binding members because serial dilutions allow one to identify the proper analytical range for quantitative determination without *a priori* knowledge of the target or library member quantities. Therefore, the invention as a whole was *prima facie* obvious at the time it was invented.

Claims 1-3, 5-7, 11-13, 17, 18, 21-31, 33, 35, 37-39, 41-43, 44, 47, 48 and 52 are obvious over Cai, Lueking, Kay and Conklin:

Claims 1-3, 5-7, 11-13, 17, 18, 21-31, 33, 35, 37-39, 41-43, 44, 47, 48 and 52, rejected under 35 U.S.C. 103(a) as being unpatentable over Cai *et al.*, *Proc. Natl. Acad. Sci.*, *92*:6537-6541 (**1995**), in view of Lueking *et al.*, *Current Genomics*, *2*:151-159 (**2001**), as applied to claims 1-3, 5-7, 11-13, 17, 18, 21-31, 33, 35, 37-39, 43, 44, 47, 48 and 52, above, and further in view of Kay *et al.*, U.S. Patent No. 5,747,334, issued on May 5, 1998, and Conklin *et al.*, U.S. Patent No. 6,756,214, issued on June 29, 2004.

Although Cai and Lueking teach differential expression techniques using protein capture assays with phage, neither Cai nor Lueking expressly suggests denaturing the biomolecule target prior to binding the library members as in claims 41 and 42.

Kay is directed towards a method for producing heterofunctional binding fusion proteins. The binding proteins are concatenated heterofunctional proteins, polypeptides or peptides comprising at least two functional regions: a binding domain with affinity for a ligand and a second effector peptide portion that is chemically or biologically active, and are prepared by use of a phage library (col. 4, lines 25-61). Kay teaches that by treating a target protein with a denaturant prior to binding an antibody, one can determine if the binding interaction with an antibody is a function of the selectivity for a discontinuous epitope (col. 61, lines 21-40).

Conklin is directed towards certain polypeptides and the antibodies that specifically bind to the polypeptides. Conklin explains that the peptides may bear either a linear or discontinuous epitope, and that antibodies that recognize, for example, linear epitopes are particularly useful in analytical and diagnostic applications that utilize denatured protein targets. It is noted that this approach finds particular usefulness in applications of analysis of protein targets from whole cells, body fluid samples or culture media (col. 5, line 64 through col. 6, line 17).

One of ordinary skill in the art would have had a reasonable expectation of success in arriving at the invention as claimed because each of Cai, Lueking, Kay and Conklin are directed towards the use of analytical assays for targeting a biomolecule using a selective binding member, such as an antibody or peptide displayed via phage. One of ordinary skill in the art would have motivated to first denature the biomolecule target as taught by Kay and/or Conklin with the methods of Cai and Lueking because of the advantages of being able to characterize the type of epitope binding interaction, and/or for the advantages in working with unknown samples where the sample is either whole cells, body fluid samples or culture media. Therefore, the invention as a whole was *prima facie* obvious at the time it was invented.

Claims 1-3, 5-7, 11-13, 17, 18, 21-31, 33, 35, 37-39, 43, 44, 46-48 and 52 are obvious over Cai, Lueking and Hoogenboom:

Claims 1-3, 5-7, 11-13, 17, 18, 21-31, 33, 35, 37-39, 43, 44, 46-48 and 52, rejected under 35 U.S.C. 103(a) as being unpatentable over Cai *et al.*, *Proc. Natl. Acad. Sci.*, *92*:6537-6541 (**1995**), in view of Lueking *et al.*, *Current Genomics*, *2*:151-159 (**2001**), as applied to claims 1-3, 5-7, 11-13, 17, 18, 21-31, 33, 35, 37-39, 43, 44, 47, 48 and 52, above, and further in view of Hoogenboom *et al.*, *Immunotechnology*, *4*:1-20 (**1998**).

Although Cai and Lueking teach differential expression techniques using protein capture assays with phage and disclose the use of chips as the capture platform, neither Cai nor Lueking expressly suggests using a column as in claim 46.

Hoogenboom is directed towards a review of phage display technology and applications in molecular biology. Hoogenboom teaches common aspects in phage display technology that involve the selection of the solid support for immobilizing the target in order to perform the panning process for the enrichment of phage that bind to the target with the highest affinity.

Amongst the supports (or matrix) that are taught in Hoogenboom, are included general solid supports, sensor chips, cells and columns (page 8, col. 2, first paragraph in section, *4.1 Diversity in selection methods*).

One of ordinary skill in the art would have had a reasonable expectation of success in arriving at the invention as claimed because each of Cai, Lueking and Hoogenboom are directed towards the use of phage library for differential expression profiling. One of ordinary skill in the art would have recognized from the disclosure of Hoogenboom that columns, like the chips of Lueking, are well-known supports used for differential capture, and that can provide the additional advantage of having an increased target loading due to the increased surface are that columns provide over chips. Therefore, the invention as a whole was *prima facie* obvious at the time the invention was made.

Requirement Under 37 C.F.R. § 1.78(c)

Claims 1-31, 33, 35, 37-48, 50 and 52 directed to an invention not patentably distinct from claims 1-49 of commonly assigned U.S. Patent No. 7,208,268, nor are they patently distinct from claims 1-53 of pending U.S. Application 11/789,469. The comparison of the presently claimed invention and the other claimed inventions are detailed in the rejection below.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned U.S. Patent No. 7,208,268, and U.S. Application No. 11/789,469, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly

assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claims because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR § 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR § 3.73(b).

Double Patenting Rejection over the claims of the '268 patent, the '469 application, Cai, Lueking and Fowlkes:

Claims 1-31, 33, 35, 37-48, 50 and 52, are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-49 of U.S. Patent No. 7,208,268, in view of Cai, Lueking and Fowlkes.

Claims 1-31, 33, 35, 37-48, 50 and 52 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-53 of copending Application No. 11/789,469 in view of Cai, Lueking and Fowlkes. This is a provisional obviousness-type double patenting rejection.

Although the conflicting claims are not identical, they are not patentably distinct from each other because claim 1 of the instant patent, is directed towards a method for determining an abundance of a biomolecule in a biological sample, said method comprising the steps of: (a) adhering a first biological sample to a first support to create a first matrix comprising one or more biomolecules from said first sample; (b) adhering a second biological sample to a second support to create a second matrix comprising one or more biomolecules from said second sample; (c) exposing a library of binding species at least one time to said first matrix to create a first product comprising one or more binding species of said library; and (d) exposing the first product at least one time to said second matrix to create a second product, wherein a binding species present or absent in said second product is indicative of the abundance of said biomolecule in said first biological sample relative to said second biological sample. Claims 2-6 are directed towards preparing further products and binding comparisons. Claims 29-31, 33, 35 and 37 are directed towards various tissues and samples.

Claim 1 of the '268 patent is directed towards a method of identifying differences in expression of polypeptides between two samples, said method comprising: (a) providing one or more first arrays comprising one or more polypeptides from a first complex biological sample adhered to a first type of support; (b) providing one or more second arrays comprising one or more polypeptides from a second complex biological sample adhered to a second type of support; (c) exposing a peptide-nucleic acid coupled library comprising a plurality of members (i) to one of said first arrays at least one time to create a first product, said first product comprising one or more members of said peptide-nucleic acid coupled library that reversibly bind to said first array and (ii) to one of said second arrays at least one time to create a third product, said third product comprising one or more members of said peptide-nucleic acid

coupled library that reversibly bind to said second array; (d) exposing said first product to one of said second arrays at least one time to create a second product, said second product comprising one or more members of said first product that do not bind to said second array and; (e) exposing said third product to one of said first arrays at least one time to create a fourth product, said fourth product comprising one or more members of said third product that do not bind to said first array, wherein a member of said peptide-nucleic acid coupled library in said second product binds to a polypeptide in said first biological complex sample that is expressed in a greater amount than in said second complex biological sample and a member of said peptide-nucleic acid coupled library in said fourth product binds to a polypeptide in said second biological sample that is expressed in a greater amount than in said first biological sample. claims 2-6 of the '268 patent is directed towards further binding comparisons.

Claim 1 of the '469 application is directed towards a method of identifying a polypeptide, said method comprising: (a) adhering a complex biological sample from a first type of individual to a support to create an array; (b) adhering a complex biological sample from a second type of individual to a support to create an array; (c) exposing a peptide-nucleic acid coupled library at least one time to an array formed by step (a) to create a first product; and (d) exposing said first product at least one time to an array formed by step (b) to create a second product. Claims 2-7 of the '469 application are not patently distinct from claims 2-6 of the instant application.

Although the related claims of the '268 patent and the '469 application are directed towards differential expression techniques using protein capture assays with phage, the claims do not expressly suggest using the claimed dilutions in the determination steps as in claims 7-10 and 14-16, nor the derivatizing limitations of claims 23 and 25.

Lueking provides a review of proteomics research, including a discussion of the methods used in the art to characterize the differential expression of proteins between two different tissues, such as healthy and diseased tissues (page 152, paragraph bridging columns 1 and 2), including subtracted library generation. Lueking also discusses how immunoassays are used to quantify the corresponding target/antigen using libraries of antibodies or phage (page 156, column 1, first full paragraph), and the application with protein arrays (page 157, column 2, final paragraph). As in claim 7, Lueking teaches the use of a protein array with dilutions of the biological matrix (page 155, col. 2, near the bottom of the column).

As in claim 21, Lueking teaches that the biomolecules are proteins, such as the proteins in a protein array (page 152, col. 2). As in claims 22 and 24, Lueking teaches that the biomolecules of the profile being studied are attached to the surface of the bioassay device (Lueking, page 154, col. 1, second full paragraph – wherein Yang is cited for attachment;[2] Yang teaches that biomolecules are first derivatized with streptavidin for binding to biotinylated surfaces, or biotin-streptavidin-biotin attachment). As in claims 23 and 25, the extent of the derivatization (*i.e.*, density) is controlled by the type of derivatizing agent (Lueking's reference to Yang, Yang at page 1754, paragraph bridging cols. 1 and 2). In this same section Lueking, Lueking also teaches covalent attachment of the biomolecules to the support matrix.

Fowlkes is directed to the identification of compounds in a compound library which can mediate the biological activity of a target receptor protein, wherein the library members include phage. Fowlkes teaches the use of phage in a panning experiment for identifying members that bind to a given series of targets, wherein the phage are then bound to the immobilized DH5αF' through a series of dilutions (col. 34, lines 42-57). In doing so, Fowlkes is able to find the appropriate analytical ranges for titer approximation.

One of ordinary skill in the art would have had a reasonable expectation of success in arriving at the invention as claimed because each of the '268 patent, the '469 application, Cai, Lueking and Fowlkes are directed towards the use of phage libraries for identifying target binding partners. One of ordinary skill in the art would have recognized advantages of the derivatization optimizing approach of Lueking for providing an improved target-bound support, as well as the advantages of Fowlkes with the approach of Stroobant and Lueking for analyzing the target binding members because serial dilutions allow one to identify the proper analytical range for quantitative determination without *a priori* knowledge of the target or library member

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[2] Since Yang (Yang *et al.*, *Langmuir*, *16*:1751-1758 (**2000**)) is effectively incorporated by reference into the teaching of Lueking, in particular the teachings as it pertains to derivatizing biomolecules for immobilization, Lueking is treated as teaching these limitations. *See*, *Advanced Display Systems Inc. v. Kent State University*, 54 USPQ2d 1673 at 1679 (Fed. Cir. 2000) – "Incorporation by reference provides a method for integrating material from various documents into a host document --a patent or printed publication in an anticipation determination-- by citing such material in a manner that makes clear that the material is effectively part of the host document as if it were explicitly contained therein. *In re Saunders*, 444 F.2d 599, 602-03, 170 USPQ 213, 216-17 (CCPA 1971) (reasoning that a rejection for anticipation is appropriate only if one reference "expressly incorporates a particular part" of another reference.

quantities. Therefore, the invention as whole was *prima facie* obvious at the time it was invented.

Claim Rejections - 35 USC § 102 as required by 37 C.F.R. § 1.78(c)

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The claims are anticipated by Stroobant – common inventor/common assignee:

Claims 1-6, 11-13, 17-22, 24, 26-31, 33, 35, 37-48, 50 and 52 are rejected under 35 U.S.C. 102(e) as being unpatentable over Stroobant, U.S. Patent No. 7,208,268, issued on April 24, 2007, and the published application from which this patent issued, U.S. Patent Application Publication No. 2002/0090637 A1, published on July 11, 2002.

The applied reference has a common inventor and assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome

by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

As in claim 1, Stroobant teaches a method for determining an abundance of a biomolecule in a biological sample, said method comprising the steps of: (a) adhering a first biological sample to a first support to create a first matrix comprising one or more biomolecules from said first sample; (b) adhering a second biological sample to a second support to create a second matrix comprising one or more biomolecules from said second sample; (c) exposing a library of binding species at least one time to said first matrix to create a first product comprising one or more binding species of said library; and (d) exposing the first product at least one time to said second matrix to create a second product, wherein a binding species present or absent in said second product is indicative of the abundance of said biomolecule in said first biological sample relative to said second biological sample (see Figure 1-10, especially Figures 9 and 10, and description thereof – see Summary of the Invention, and especially claims 1-6). The embodiments claims of 2-6, 11-13, 17-21, 38-45, 48, 50 and 52, also read on Stroobant; see the same figures and description thereof. As in claims 22 and 24, Stroobant teaches derivatizing the column (col. 7, lines 7-24). As in claims 26-28, Stroobant teaches a phage display library of recombinant phage (col. 3, lines 40-44). As in claims 29-31, 33, 35, and 37, Stroobant teaches these tissues, states and organisms (col. 3, line 5, through col. 4, line 53). As in claims 46 and 47, Stroobant teaches chips and columns (col. 4, lines 54-67).

The claims are obvious over Stroobant, Lueking and Fowlkes:

Claims 1-31, 33, 35, 37-48, 50 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stroobant, in view of Lueking and Fowlkes.

The limitations of 1-6, 11-13, 17-22, 24, 26-31, 33, 35, 37-48, 50 and 52 and the corresponding teaching in Stroobant is detailed above, and hereby incorporated into the instant rejection.

Although Stroobant teaches differential expression techniques using protein capture assays with phage, Stroobant does not expressly suggest using the claimed dilutions in the

determination steps as in claims 7-10 and 14-16, nor the derivatizing limitations of claims 23 and 25.

Lueking provides a review of proteomics research, including a discussion of the methods used in the art to characterize the differential expression of proteins between two different tissues, such as healthy and diseased tissues (page 152, paragraph bridging columns 1 and 2), including subtracted library generation. Lueking also discusses how immunoassays are used to quantify the corresponding target/antigen using libraries of antibodies or phage (page 156, column 1, first full paragraph), and the application with protein arrays (page 157, column 2, final paragraph). As in claim 7, Lueking teaches the use of a protein array with dilutions of the biological matrix (page 155, col. 2, near the bottom of the column).

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[3] Since Yang (Yang *et al.*, *Langmuir*, *16*:1751-1758 (**2000**)) is effectively incorporated by reference into the teaching of Lueking, in particular the teachings as it pertains to derivatizing biomolecules for immobilization, Lueking is treated as teaching these limitations. *See*, *Advanced Display Systems Inc. v. Kent State University*, 54 USPQ2d 1673 at 1679 (Fed. Cir. 2000) – "Incorporation by reference provides a method for integrating material from various documents into a host document --a patent or printed publication in an anticipation determination-- by citing such material in a manner that makes clear that the material is effectively part of the host document as if it were explicitly contained therein. *In re Saunders*, 444 F.2d 599, 602-03, 170 USPQ 213, 216-17 (CCPA 1971) (reasoning that a rejection for anticipation is appropriate only if one reference "expressly incorporates a particular part" of another reference.

through a series of dilutions (col. 34, lines 42-57). In doing so, Fowlkes is able to find the appropriate analytical ranges for titer approximation.

One of ordinary skill in the art would have had a reasonable expectation of success in arriving at the invention as claimed because each of Stroobant, Lueking and Fowlkes are directed towards the use of phage libraries for identifying target binding partners. One of ordinary skill in the art would have recognized advantages of the derivatization optimizing approach of Lueking for providing an improved target-bound support, as well as the advantages of Fowlkes with the approach of Stroobant and Lueking for analyzing the target binding members because serial dilutions allow one to identify the proper analytical range for quantitative determination without *a priori* knowledge of the target or library member quantities. Therefore, the invention as whole was *prima facie* obvious at the time it was invented.

Conclusions

No claim is allowable.

If Applicants should amendment the claims, a complete and responsive reply will clearly identify where support can be found in the disclosure for each amendment. Applicants should point to the page and line numbers of the application corresponding to each amendment, and provide any statements that might help to identify support for the claimed invention (*e.g.*, if the amendment is not supported *in ipsis verbis*, clarification on the record may be helpful). Should Applicants present new claims, Applicants should clearly identify where support can be found in the disclosure.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Jeff Lundgren whose telephone number is 571-272-5541. The Examiner can normally be reached from 7:00 AM to 5:30 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, James (Doug) Schultz, can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Jeffrey S. Lundgren/
Patent Examiner, Art Unit 1639